REMARKS

Applicants have amended the claims to more particularly define the invention taking into consideration the outstanding Official Action. Applicants note with appreciation the Examiner's indication of allowable subject matter in that claim 3 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claim 3 is restricted to the specific compound recited therein. This same allowable compound is specified in claims composition claim 10 and method of use claim 32. Since claims 10 and 32 are restricted to a composition containing the allowed compound and a use of the allowed compound, these claims should equally be allowable and early notification there is most respectfully requested.

Applicants would appreciate an acknowledgment of the claim for priority and receipt of the priority document to complete the claim for priority.

Applicants have amended claims 1, 7 and 25 and have canceled claims 6, 12 and 13 from the present application without prejudice or disclaimer in an effort to expedite the prosecution to early allowance. Applicants submit that the claims now present in the application are fully supported by the specification as originally filed and no new matter is introduced.

The rejection of claims 1, 6-7, 12-13, 25 and 31 under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement has been carefully considered but is most respectfully traversed in view of the amendments to the claims and the following comments.

Claim 1 has been amended to replace "or a pharmaceutically acceptable solvate thereof" with "or a pharmaceutically acceptable hydrate thereof", based on claim 6 as previously on file. Claim 6 which was directed to the hydrates has been canceled as redundant in view of this amendment. As noted in MPEP § 2164.04 the burden is on the Examiner to establish a reasonable basis to question enablement provided for the claimed invention. It is not believed that this burden has been met for the presently amended claimed subject matter. Clearly, one of ordinary skill in the art would appreciate that the term "hydrate" is where the solvent is, by definition, water.

With respect to the term "hydrate", Applicants submit that the claimed pamoate salts are polar compositions which can be expected to be solvated, to at least some degree, by a polar solvent such as water. This is confirmed, for example, by Berge *et al* (cited by the Examiner) which states on page 2, column 2, second paragraph, that salts of a basic drug with a dicarboxylic acid (pamoic acid being an aromatic dicarboxylic acid) are generally water soluble, albeit that in the case of certain basic drugs pamoic acid forms only a slightly soluble (but note still soluble) salt. It follows also that the claimed pamoate salts should have similar pharmacological effects if administered in the anhydrous or hydrated form, since the anhydrous form will become hydrated on exposure to water in the gut/blood stream. Therefore, there is no reason to conclude that one skilled in the art would have difficulty in manufacturing or using the claimed Pamoate salts in hydrate form. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claims 7-8, 12 and 25 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention has been carefully considered but is most respectfully traversed in view of the amendments to the claims and the following comments. Applicants have amended claims 7-8 and 25 in accordance with the Examiner's helpful suggestion and claim 12 has been canceled from the present application. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The objection to claims 12-13 under 37 CFR 1.75 as being a substantial duplicate of claims 1, 4-5 has been obviated in view of the cancellation of these claims from the present application without prejudice or disclaimer. Accordingly, it is most respectfully requested that this objection be withdrawn.

The objection to claim 3 as being dependent upon a rejected base claim, but otherwise allowable, has been carefully considered but is most respectfully traversed in view of the amendments to the claims. Accordingly, it is most respectfully requested that this objection be withdrawn.

The rejection of claims 25-30 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement has been carefully considered but is

most respectfully traversed in view of the amendments to the claims and the following comments.

The Examiner states that there is no definition of the term "stress-related affective disorder" in the art, but goes on to acknowledge that an "affective disorder" is a recognised psychiatric disorder and that it is known that stress may develop affective disorders. Applicants most respectfully submit that it would be apparent to one of ordinary skill in the art that a "stress related affective disorder" is therefore an affective disorder which has developed from stress, in particular a disorder such as listed in Claim 26/ paragraph [0033] of the US application as published and page 5 of the present specification.

As the Examiner rightly notes, paragraph [0033] also states that the term "stress-related affective disorder" is intended to include any disorder associated with elevated levels of 5-HT resultant from newly synthesised 5-HT. However, Applicants do not see why this statement would be considered "incredible" to one of ordinary skill in the art as the Examiner suggests. It is known from the art that the compounds of Formula I (the formula in Claim 1) act by selectively blocking tryptophan hydroxylase, and thus function by blocking new synthesis of 5-HT (see paragraphs [0007] and [0034] of the application as published). Likewise, it is known from the art that, in doing so, the compounds of Formula I have been demonstrated to have a positive effect on a variety of stress-related affective disorders, especially (but not exclusively) anxiety and depression (see paragraph [0007]). Therefore, it seems only logical to one of ordinary skill in the art to conclude that the claimed compounds may have beneficial therapeutic and/or prophylactic effects on any disorder identified as being induced by elevated levels of 5-HT resultant from newly synthesised 5-HT.

The term "stress-related affective disorder", and the various clinical conditions listed in Claim 26, are also recited in the granted bisulphate application (USSN 10/486925), so the Examiner's objection is also directly contradictory to that taken by the USPTO in this earlier application. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claims 7-13, 25-33 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement has been carefully considered but

is most respectfully traversed in view of the amendments to the claims and the following comments.

The Examiner indicates that there is no evidence on record that the claimed pamoate salts have activity beyond that of the basic drug so as to be able to treat the diversity of disorders of claim 26 or unspecified scope of claim 25. However, the applicant is not suggesting that the pamoate salts have activity beyond that of the basic drug, insofar as the range of conditions to be treated are concerned and as would be appreciated by one of ordinary skill in the art to which the invention pertains.

To the contrary, and as outlined above, it is known from the art that the compounds of Formula I (the formula in Claim 1) act by selectively blocking tryptophan hydroxylase and can be used to treat a variety of stress-related affective disorders. For example, the patents acknowledged at paragraph [0007] of the present published application refer to treatment of migraines, depression, anxiety, Kleine-Levin syndrome, sleep apnoea, sudden infant death syndrome, anxiogenisis associated with drug withdrawal, cognitive deficiencies, and senile dementia. Indeed, US 4,835,151 and 4,461,771, cited by the Examiner, themselves teach that abnormally high 5HT levels are present in a variety of affective disorders (see column 2 of both patents), and that the compounds of Formula I reduce 5-HT turnover by blocking tryptophan hydroxylase, and have anxiolytic activity (see column 3 of both patents).

Therefore, the use of the claimed pamoate salts to treat stress-related affective disorders in general, and the conditions claimed in claim 26 in particular, is Applicants submit consistent with the teaching in the art as to the known effects of the basic drug. Accordingly, it is most respectfully requested that this rejection be withdrawn.

Applicants most respectfully submit that all of the claims now present in the application are in full compliance with 35 USC 112 and clearly patentable over the references of record.

The rejection of claims 1-2, 4-9, 11-13, 25-31 and 33 under 35 USC 103(a) as being unpatentable over Gittos et al. US 4,835,151 or US 4,461,771 supplemented with RN 103353-87-3 in view of Berg et al. has been carefully considered but is most respectfully traversed in view of the amendments to the claims and the following comments.

US 4,835,151 and 4,461,771 have already been acknowledged in the present application (paragraph [0007] of the US application as published), and teach that the compounds of Formula I, in a variety of salt forms (not including the pamoate) can be used to treat a variety of stress-related affective disorders. RN 103353-87-3 discloses the chemical structure of the preferred compound of Formula I, referred to as AGN 2979, which compound is also already acknowledged in paragraph [0007] as being known. The article by Berge *et al* merely discusses general criteria to be adopted in selecting suitable salt forms of known pharmaceutical actives.

There is no teaching in any of the cited documents of a pamoate salt of the compounds of Formula I in general, or of AGN 2979 in particular, and therefore there is no teaching of a pamoate salt as claimed in claim 1 of the present application.

Of the compounds taught in US 4,461,711 and US 4,835,151, the compound of choice for clinical investigation was AGN 2979 in the hydrochloride salt form. Subsequent animal studies with AGN 2979 HCl showed unacceptable toxicity levels, as a result of which the US Food and Drugs Administration precluded the use of the compound in the levels previously shown to be pharmaceutically effective (again, see paragraphs [0007] and [0008] of the present published application).

Although no other compounds according to Formula I were apparently tested, given that Formula I only covers a few other compounds (the only variables are R_1, R_2, and n, with R_1 and R_2 being selected from methoxy, ethoxy, hydroxy or hydrogen, and n being 2 or 3), it was and is to be expected that the effects of the other compounds will be similar. Indeed, the very fact that no other compounds were tested demonstrates that those testing AGN 2979 expected the toxic effects to extend to these other compounds as would be appreciated by one of ordinary skill in the art. Likewise, while only the HCl salt form was tested, this is again because it was expected that other salt forms would have similar toxic effects. The fact that US 4,461,711 and US 4,835,151 refer to various salts, *including the HCl salt*, as being "pharmaceutically acceptable" in no way contradicts the above, since these patents were drafted prior to the FDA withdrawal of clinical approval for AGN 2979 HCl. Once it became clear that the HCl salt form was <u>not</u> "pharmaceutically acceptable", it was evident that the statement in US

4,461,711 and US 4,835,151 regarding various salt forms being "pharmaceutically acceptable" could not be relied upon.

Contrary to the above expectations, the present application discloses (see paragraph [0009] as published) that by using the pamoate salt form of the compounds of Formula I the problem of toxicity is overcome. Thus, the presently claimed pamoate salts can be used to treat the indications for which the previously known hydrochloride salts were used, without the toxicity of the previously known hydrochloride salts. This overcomes a long standing problem in the art (the toxicity of the hydrochloride salt of AGN 2979 having been known for over a decade), and therefore does indeed represent an unexpected and highly beneficial result which could not have been obviously predicted.

More specifically, there is no teaching in the art that would have lead one of ordinary skill in an obvious manner to attempt the use of the pamoate salt form as a means for overcoming the unacceptable toxicity of the previously known hydrochloride salts. In particular, there is no teaching in Berge *et al* that the pamoate salt form could be expected to be less toxic. To the contrary, Berge acknowledges that the task of choosing an appropriate salt can be very difficult (see page 1, first paragraph), and notes that in general the hydrochloride salt form of a pharmaceutical is by far and away the most often used salt form (see table 1, where it is indicated that the hydrochloride salts had, at the date of publication of Berge, been used in 42.98% of the anion salts approved by the FDA for pharmaceutical use). Thus, the teaching of Berge in fact illustrates the magnitude of the problem faced by one skilled in the art. The skilled person knew that the most often used salt form, namely the hydrochloride salt form, had in the case of the compounds disclosed in US 4,461,711 and US 4,835,151 been found to be unacceptably toxic. There could have been no expectation that any other salt form would be less toxic, nor was there any obvious indication as to what other salt forms should be used if an attempt were to be made to find a less toxic salt form. It would therefore not have been obvious to one skilled in the art to make or use the presently claimed pamoate salts.

In support of the asserted lack of toxicity associated with the claimed pamoate salts, Applicants also enclose herewith data demonstrating that AGN 2979 Pamoate did

not produce any toxic effects in a rat study (the previous toxic effects of AGN 2979 having manifested themselves in a similar such study). Applicants do not at this stage have any test data with regard to the other compounds of Formula I, and will therefore have to rely on the fact that the other compounds represent only minor variations (as discussed above). Accordingly, it is most respectfully requested that this rejection be withdrawn.

In view of the above comments and further amendments to the claims, favorable reconsideration and allowance of all the claims now present in the application are most respectfully requested.

Respectfully submitted,
BACON & THOMAS, PLLC

By: Richard E. Fichter
Richard E. Fichter
Registration No. 26,382

625 Slaters Lane, Fourth Floor
Alexandria, Virginia 22314
Phone: (703) 683-0500
Facsimile: (703) 683-1080
REF/cjw
A01.wpd
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